Osteoarthritis and Cartilage 23 (2015) 874–881

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Joint space narrowing, body mass index, and knee pain: the ROAD study (OAC1839R1)

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ARTICLE INFO

Article history:
Received 16 July 2014
Accepted 20 January 2015

Keywords:
Cohort study
Epidemiology
Osteoarthritis
Pain

SUMMARY

Objective: The objective of the present study was to clarify the association of joint space narrowing with knee pain in Japanese men and women using a large-scale population-based cohort of the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study.
Methods: This study examined the association between minimum joint space width (mJSW) in the medial compartment and pain at the knee. mJSW was measured in the medial and lateral compartments of the knee using a knee osteoarthritis (OA) computer-aided diagnosis system.
Results: From the 3040 participants in the ROAD study, the present study analyzed 2733 participants who completed the radiographic examinations and questionnaires regarding knee pain (975 men and 1758 women; mean age, 69.9 ± 11.2 years). Subjects with lateral knee OA were excluded. After adjustment for age and Body mass index (BMI), medial mJSW, as well as medial mJSW/lateral mJSW, was significantly associated with knee pain. Sex and BMI affected the association of medial mJSW with knee pain. The threshold of medial mJSW was approximately 3 mm in men and 2 mm in women, while that of medial mJSW/lateral mJSW was approximately 60% in both men and women. BMI was found to have a distinct effect on the association of mJSW with pain.
Conclusion: The present cross-sectional study using a large-scale population from the ROAD study showed that joint space narrowing had a significant association with knee pain. The thresholds of joint space narrowing for knee pain were also established.

Introduction

Knee osteoarthritis (OA) is a major public health issue that causes chronic pain and disability[1–3]. The prevalence of radiographic knee OA is high in Japan [4], with 25,300,000 persons aged 40 years and older estimated to have radiographic knee OA[5]. According to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities that subsequently require support with activities of daily living[6].

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http://dx.doi.org/10.1016/j.joca.2015.01.011
1063-4584/

Knee pain is the principal clinical symptom of knee OA[7]. Although much effort has been devoted toward a definition of knee pain, the correlation with radiographic severity of the knee OA was not as strong as one would expect[4,8–10]. One of the reasons for this apparent discrepancy may be the definition of knee OA. Kellgren Lawrence (KL) grading is the conventional system most used to grade the radiographic severity of knee OA[11], but in this categorical system, joint space narrowing is not assessed separately. A recent cross-sectional study showed that the association between joint space narrowing and osteophytosis was not as high as expected on plain radiographs[12]. In addition, joint space narrowing and osteophytosis had distinct effects on QOL[12]. These accumulating lines of evidence have indicated that joint space narrowing and osteophytosis may have distinct etiologic mechanisms, and their progression may be neither constant nor proportional. Although osteophytosis also has some effect on ADL and QOL[12], joint space narrowing is the primary outcome in studies of OA[13]. Thus, to examine the association between knee OA and pain, joint space narrowing should be assessed separately. Chan *et al.* examined the association of joint space narrowing and duration of pain in patients with knee OA and found a significant association[14], but joint space narrowing was defined by categorical methods. Because categorical methods are statistically less powerful than continuous methods, the association between pain and knee OA might have been underestimated. To overcome this, a fully automatic system that can quantify the joint space width of knee OA on standard radiographs and allows for objective, accurate, and simple assessment of the structural severity of knee OA was developed[15]. Thus far, Kinds *et al.* measured joint space width and found significant associations with clinical outcomes[16], but the threshold of joint space width for clinical outcomes remains unclear.

Sex differences have been observed in knee OA. The prevalence of knee OA is higher in women than men, and the association of knee pain with knee OA also differs by sex[4]. Thus, the impact of joint space narrowing and osteophytosis on QOL may also differ between the sexes. Obesity is also one of the few established risk factors for knee OA and pain[17–23]. This suggests that a distinct association of joint space narrowing with pain may be found in subjects with and without obesity. However, to the best of our knowledge, there are no population-based studies that assess the effect of obesity on the association of joint space narrowing with pain.

Therefore, the objective of this study was to clarify the association of joint space narrowing with pain at the knee among Japanese men and women using a fully automatic system to measure joint space width in a large-scale, population-based cohort from the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study. Furthermore, the threshold of minimum joint space width (mJSW) or medial mJSW/lateral mJSW for pain was determined using receiver operating characteristic (ROC) curve analysis.

Subjects and methods

Subjects

The ROAD study is a nationwide prospective study designed to establish epidemiologic indices for the evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (with OA and osteoporosis as the representative bone and joint diseases). It consists of population-based cohorts in several communities in Japan. A detailed profile of the ROAD study has been reported elsewhere[4,5,24], and, thus, only a brief summary is provided here. To date, we have completed the creation of a baseline database including clinical and genetic information for 3040 inhabitants (1061 men and 1,979 women) ranging in age from 23 to 95 years (mean, 70.3 years), who were recruited from resident registration listings in three communities: an urban region in Itabashi, Tokyo, a mountainous region in Hidakagawa, Wakayama, and a coastal region in Taiji, Wakayama. All participants provided their written, informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Anthropometric measurements, including height and weight, were taken, and body mass index (BMI; weight [kg]/height^2 [m^2]) was calculated. Furthermore, all participants were also interviewed by well-experienced orthopedists regarding pain in both knees, by asking: “Have you experienced right knee pain on most days in the past month, in addition to now?” and “Have you experienced left knee pain on most days in the past month, in addition to now?”. Subjects who answered “yes” were defined as having knee pain. Among the 3040 subjects who participated in the baseline study, 30 (1.0%) who underwent unilateral or total knee arthroplasty were excluded. In addition, 35 (1.1%) whose radiographic examinations were insufficient for measuring joint space width, and 195 (6.4%) with lateral knee OA were excluded. One reason for excluding lateral knee OA is that most knee OA in Japan is medial type[4]. The other reason is that medial and lateral knee OA have distinct characteristics, and joint space narrowing occurs in the medial compartment in medial knee OA, but medial joint space width may not change or be larger in lateral knee OA. Furthermore, 47 patients (1.5%) who provided incomplete questionnaires regarding pain and so on were excluded, leaving a total of 2733 (89.9%) subjects (975 men and 1758 women).

Radiographic assessment

All participants underwent radiographic examinations of both knees using an anterior-posterior view with weight-bearing and foot map positioning by experienced radiological technologists. The beam was positioned parallel to the floor with no angle and aimed at the joint space. To visualize the joint space properly and to centralize the patella over the lower end of the femur, fluoroscopic guidance with an anterior-posterior X-ray beam was used, and the images were downloaded into Digital Imaging and Communication in Medicine (DICOM) format files. Knee radiographs were read without knowledge of participant clinical status by a single experienced orthopedist (S.M.) using the KL radiographic atlas for overall knee radiographic grades[11], and knee OA was defined as KL grade 2 or greater. The KOACAD system was used to measure mJSW in the medial compartment and OPA at the medial tibia[15], and the knee with the lower mJSW was defined as the designated knee for a participant. The KOACAD system is a fully automatic system that can quantify the major features of knee OA on standard radiographs and allows for objective, accurate, and simple assessment of the structural severity of knee OA in general clinical practice. This system was programmed to measure mJSW in the medial and lateral compartments using digitized knee radiographs. The KOACAD system has been described in detail elsewhere[15,25]. The KOACAD system was applied to the DICOM data by the experienced orthopedist who developed this system (H.O.); measurement reliability has been shown to be good[15], and the intraclass coefficient of correlation for medial mJSW measured on radiographs for an individual with weight-bearing and foot map positioning was 0.96. Reference values for OPA and mJSW by sex and age strata in Japan using the KOACAD system have been published previously[25]. Lateral knee OA was defined as KL grade 2 or greater with lower lateral mJSW than medial mJSW.

Statistical analysis

Differences in age, height, weight, BMI, mJSW, and medial/lateral mJSW between men and women and between subjects with and

without pain were examined by the non-paired Student's *t*-test. The prevalence of knee OA was compared between men and women by the χ^2 test. Associations of age, BMI, mJSW, and medial/lateral mJSW with knee pain were determined using multiple logistic regression analysis after adjustment for age, sex, and BMI overall, and after adjustment for age and BMI in men and women. In addition, subjects were classified according to mJSW (<1 mm, ≥1–<2 mm, ≥2–<3 mm, ≥3–<4 mm, ≥4 mm), and the associations of mJSW<1 mm, ≥1–<2 mm, ≥2–<3 mm, and ≥3–<4 mm with pain were determined using multiple logistic regression analysis after adjustment for age and BMI, compared with mJSW≥4 mm. To clarify the effect of BMI on the association of mJSW with pain, subjects were further classified into 10 groups according to mJSW and BMI (BMI <23 kg/m^2: mJSW<1 mm, ≥1–<2 mm, ≥2–<3 mm, ≥3–<4 mm, ≥4 mm; BMI ≥ 23 kg/m^2: mJSW<1 mm, ≥1–<2 mm, ≥2–<3 mm, ≥3–<4 mm, ≥4 mm), and the association with pain was determined using multiple logistic regression analysis after adjustment for age, compared with BMI <23 kg/m^2 and mJSW ≥4 mm. Subjects were also classified according to medial/lateral mJSW (<30%, ≥30–<40%, ≥40–<50%, ≥50–<60%, ≥60–<70%, ≥70–<80%, ≥80%), and the associations of medial/lateral mJSW<30%, ≥30–<40%, ≥40–<50%, ≥50–<60%, ≥60–<70%, and ≥70–<80% with pain were determined using multiple logistic regression analysis after adjustment for age and BMI, compared with medial/lateral mJSW ≥80%. The thresholds of mJSW and medial/lateral mJSW for pain were determined using ROC curve analysis. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

Results

The characteristics of the 2733 participants in the present study are shown in Table I. The prevalence of knee OA was significantly higher in women than in men. The mJSW and medial mJSW/lateral mJSW were significantly lower in women than in men. The participants in the present study were significantly younger than the non-participants ($P < 0.05$), while BMI was not significantly different between them (non-participants: age, 74.3 ± 7.9 years; BMI, 23.1 ± 3.2 kg/m^2).

Table II shows age, BMI, mJSW, and medial/lateral mJSW in subjects with and without pain. For the right knee, overall and in women, subjects with pain were older and had higher BMI, narrower mJSW, and smaller medial/lateral mJSW than those without pain. In men, subjects with pain had higher BMI, narrower mJSW, and smaller medial/lateral mJSW than subjects without pain, while age was not significantly different in men with and without pain. For the left knee, results were similar except for age in men. Associations of mJSW and medial/lateral mJSW with right and left knee pain were next examined using multiple logistic regression analysis after adjustment for age, sex, and BMI overall, and after adjustment for age and BMI in men and women (Table II). Odds ratios (ORs) of mJSW (1-mm decrease) for pain were higher than 2, and the ORs of medial/lateral mJSW (10% decrease) for pain were 1.2–1.3.

Subjects were then classified according to mJSW (<1 mm, ≥1–<2 mm, ≥2–<3 mm, ≥3–<4 mm, ≥4 mm), and the prevalence of knee pain was examined (Fig. 1, Supplementary Table I). The prevalence of knee pain was more than 60% in subjects with mJSW<1 mm, while it was less than 10% in those with mJSW ≥4 mm. The OR for pain was also calculated after adjustment for age and BMI. Men with mJSW <1 mm, ≥1–<2 mm, and ≥2–<3 mm had significantly higher rates of pain than those with mJSW ≥4 mm, but men with mJSW ≥3–<4 mm did not (Table III). The OR for pain in men with mJSW <1 mm was around 40. Women with mJSW <1 mm and ≥1–<2 mm had significantly higher rates of pain than those with mJSW ≥4 mm, but, women with mJSW ≥2–<3 mm and ≥3–<4 mm did not. The ORs for pain in women with mJSW <1 mm were 12–14. Subjects were further classified into 10 groups according to BMI and mJSW (BMI < 23 kg/m^2: mJSW < 1 mm, ≥1–<2 mm, ≥2–<3 mm, ≥3–<4 mm, ≥4 mm; BMI ≥ 23 kg/m^2: mJSW < 1 mm, ≥1–<2 mm, ≥2–<3 mm, ≥3–<4 mm, ≥4 mm), and the ORs for pain were calculated (Supplementary Table II). In men, mJSW<1 mm and ≥1–<2 mm with BMI <23 kg/m^2 and mJSW < 1 mm, ≥1–<2 mm, and ≥2–<3 mm with BMI ≥23 kg/m^2 were significantly associated with pain compared with mJSW ≥4 mm with BMI <23 kg/m^2. In women at the right knee, mJSW < 1 mm with BMI <23 kg/m^2 and mJSW ≥0–<1 mm and ≥1–<2 mm with BMI ≥23 kg/m^2 were significantly associated with pain compared with mJSW ≥4 mm with BMI <23 kg/m^2. In women at the left knee, mJSW < 1 mm and ≥1–<2 mm with BMI <23 kg/m^2 and mJSW < 1 mm, ≥1–<2 mm, and ≥2–<3 mm with BMI ≥23 kg/m^2 were significantly associated with pain compared with mJSW ≥4 mm with BMI <23 kg/m^2.

Subjects were also classified according to medial/lateral mJSW (<30%, ≥30–<40%, ≥40–<50%, ≥50–<60%, ≥60–<70%, ≥70–<80%, ≥80%), and the prevalence of knee pain was examined (Fig. 2, Supplementary Table III). The prevalence of knee pain was approximately 60% in subjects with medial mJSW/lateral mJSW < 30%, while it was approximately 10% in those with medial mJSW/lateral mJSW ≥80%. The ORs for pain were also calculated after adjustment for age and BMI (Table IV). Men and women with mJSW <30%, ≥30–<40%, ≥40–<50%, and ≥50–<60% had higher rates of pain compared with those with mJSW ≥80%, except for men with mJSW≥50–<60% at the right knee. The ORs for pain in men with mJSW <30% were 14–20. The OR for pain in women with mJSW <30% was around 10.

The threshold values of mJSW for knee pain were then determined using ROC curve analysis (Supplementary Fig. 1). In men, the threshold values of mJSW for pain at the right and left knees were 2.87 mm (sensitivity 0.67, specificity 0.65, AUC 0.70, 95% confidence interval (CI) 0.64–0.75) and 2.82 mm (sensitivity 0.62, specificity 0.67, AUC 0.72, 95% CI 0.66–0.77), respectively. In women, the threshold values of mJSW for pain at the right and left knees were 2.01 mm (sensitivity 0.43, specificity 0.689, AUC 0.69, 95% CI 0.66–0.73) and 2.44 mm (sensitivity 0.59, specificity 0.75, AUC 0.71, 95% CI 0.67–0.74), respectively. Threshold values of medial/lateral mJSW for knee pain were also determined using ROC curve analysis (Supplementary Fig. 2). In men, the threshold values of medial/lateral mJSW for pain at the right and left knees were 55.2% (sensitivity 0.45, specificity 0.68, AUC 0.66, 95% CI 0.60–0.72) and

Table I
Characteristics of the subjects in the present study

	Overall	Men	Women	*P* values
N	2733	975	1758	
Age, years	69.9 ± 11.2	70.8 ± 10.8	69.4 ± 11.4	0.0012
Height, cm	154.4 ± 8.9	162.5 ± 6.7	150.0 ± 6.4	<0.0001
Weight, kg	55.1 ± 10.3	61.4 ± 10.0	51.6 ± 8.7	<0.0001
BMI, kg/m^2	23.0 ± 3.3	23.2 ± 3.0	22.9 ± 3.5	0.0493
Right knee				
Knee OA, %	45.3	33.6	51.8	<0.0001
mJSW, mm	2.8 ± 1.0	3.2 ± 0.9	2.6 ± 0.9	<0.0001
medial mJSW/lateral mJSW, %	68.7 ± 30.1	71.1 ± 22.2	67.4 ± 33.6	0.0007
Left knee				
Knee OA, %	47.5	35.8	54	<0.0001
mJSW, mm	2.9 ± 1.0	3.3 ± 01.0	2.7 ± 0.9	<0.0001
medial mJSW/lateral mJSW, %	70.8 ± 26.3	73.9 ± 22.7	69.1 ± 28.0	<0.0001

Except where indicated otherwise, values are means ± SD.
Knee OA was defined as Kellgren Lawrence grade 2 or worse.
BMI, body mass index; OA, osteoarthritis; mJSW, minimum joint space width.

Table II
Associations of age, BMI, mJSW, and medial mJSW/lateral mJSW with knee pain

	Right knee					Left knee				
	Pain +	Pain −	Adjusted OR	95% CI	*P* values	Pain +	Pain −	Adjusted OR	95% CI	*P* values
Overall										
N										
Age, years	72.4 ± 8.6	69.3 ± 11.6*	1.01	1.00–1.03	0.0499	72.8 ± 8.4	69.3 ± 11.6*	1.01	0.99–1.02	0.3226
BMI, kg/m^2	24.4 ± 3.6	22.7 ± 3.2*	1.12	1.08–1.16	<0.0001	24.2 ± 3.5	22.8 ± 3.2*	1.10	1.06–1.14	<0.0001
mJSW, mm (1-mm decrease)	2.1 ± 1.1	2.9 ± 0.9*	2.17	1.92–2.50	<0.0001	2.2 ± 1.1	2.9 ± 0.9*	2.22	1.96–2.56	<0.0001
medial mJSW/lateral mJSW, % (10% decrease)	54.3 ± 30.7	71.9 ± 29.0*	1.30	1.24–1.37	<0.0001	56.6 ± 30.4	71.0 ± 29.5*	1.22	1.16–1.29	<0.0001
Men										
N										
Age, years	71.7 ± 9.4	70.7 ± 11.0	0.99	0.96–1.02	0.5095	72.8 ± 8.7	70.5 ± 11.0*	0.98	0.95–1.01	0.2278
BMI, kg/m^2	24.2 ± 3.0	23.0 ± 3.0*	1.09	1.01–1.18	0.0207	24.1 ± 3.1	23.0 ± 3.0*	1.08	0.995–1.17	0.0635
mJSW, mm (1-mm decrease)	2.4 ± 1.2	3.3 ± 0.9*	2.33	1.82–3.03	<0.0001	2.6 ± 1.1	3.2 ± 0.9*	2.50	1.92–3.23	<0.0001
medial mJSW/lateral mJSW, % (10% decrease)	57.2 ± 27.6	72.8 ± 20.8*	1.33	1.19–1.49	<0.0001	61.3 ± 29.6	72.3 ± 20.8*	1.28	1.15–1.43	<0.0001
Women										
N										
Age, years	72.6 ± 8.4	68.5 ± 12.0*	1.02	1.005–1.04	0.0138	72.7 ± 8.3	68.6 ± 11.9*	1.02	0.997–1.04	0.0964
BMI, kg/m^2	24.4 ± 3.7	22.5 ± 3.3*	1.12	1.08–1.17	<0.0001	24.3 ± 3.6	22.6 ± 3.4*	1.11	1.06–1.16	<0.0001
mJSW, mm (1-mm decrease)	2.0 ± 1.1	2.8 ± 0.8*	2.13	1.82–2.50	<0.0001	2.1 ± 1.1	2.7 ± 0.8*	2.17	1.85–2.56	<0.0001
medial mJSW/lateral mJSW, % (10% decrease)	52.2 ± 31.5	71.4 ± 33.0*	1.30	1.22–1.38	<0.0001	55.1 ± 30.6	70.3 ± 33.7*	1.21	1.14–1.28	<0.0001

*$P < 0.05$ by non-paired Student's *t*-test.
Adjusted ORs were calculated by multiple logistic regression analysis after adjustment for age, sex, and BMI overall and after adjustment for age and BMI in men and women.
BMI, body mass index; mJSW, minimum joint space width; OR, odds ratio; CI, confidence interval.

57.9% (sensitivity 0.49, specificity 0.84, AUC 0.70, 95% CI 0.64–0.76), respectively. In women, the threshold values of medial/lateral mJSW for pain at the right and left knees were 57.9% (sensitivity 0.57, specificity 0.75, AUC 0.69, 95% CI 0.66–0.73) and 57.7% (sensitivity 0.58, specificity 0.76, AUC 0.71, 95% CI 0.68–0.74), respectively.

Discussion

Joint space narrowing is the primary outcome in studies of knee OA[20], because cartilage damage, which is one of the main causes of knee symptoms, is seen as a smaller mJSW[16]. Previous studies have shown significant associations of joint space narrowing with pain[14,16], though the threshold of joint space width for pain remained unclear. This is the first study to clarify the effect of joint space narrowing on knee pain using a large-scale, population-based, cohort study. In addition, joint space narrowing was evaluated not by categorical grade but by continuous values, using mJSW at the knee. In the present study, mJSW < 3 mm in men and mJSW < 2 mm in women were significantly associated with knee pain, compared with mJSW ≥4 mm, and the OR of mJSW < 1 mm for knee pain was quite high, particularly in men. It was also found that the effect of mJSW on pain was affected by BMI. Medial mJSW/lateral/mJSW < 60% was also significantly associated with knee pain in men and women, compared with medial mJSW/lateral mJSW ≥ 80%. Using ROC curve analysis, the thresholds of mJSW in men and women were found to be approximately 3 mm in men and

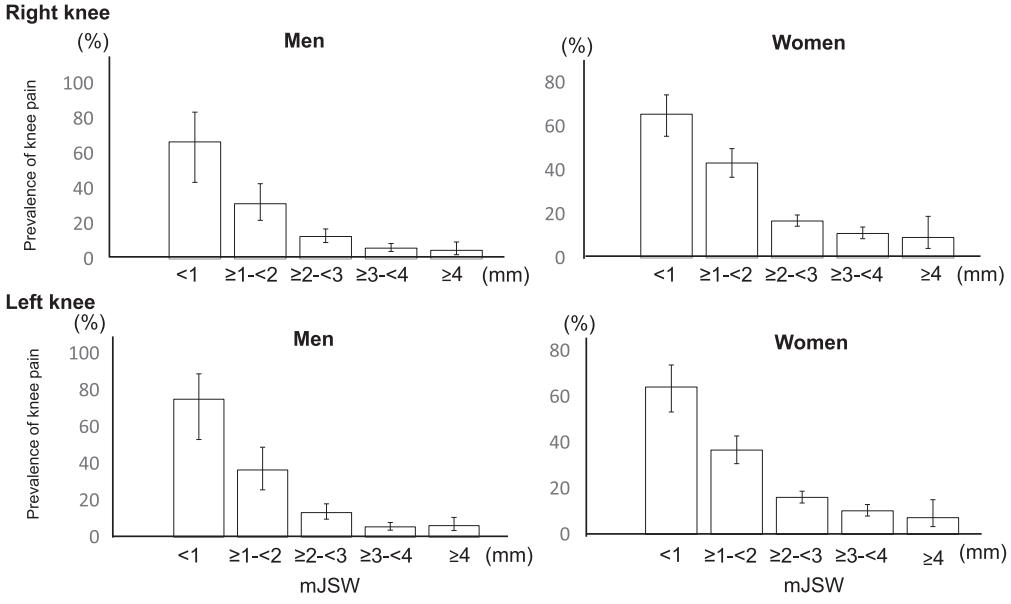

Fig. 1. Prevalence of knee pain by mJSW (mm) in men and women. mJSW, minimum joint space width.

Table III
OR of knee pain by medial mJSW

	Men				Women			
	Crude OR	95% CI	Adjusted OR	95% CI	Crude OR	95% CI	Adjusted OR	95% CI
Right knee								
<1 mm	39.0	11.9–146.4	39.4	11.6–151.8	18.4	7.7–51.9	12.3	5.0–35.3
≥1–<2 mm	9.0	3.8–23.9	8.5	3.5–23.0	7.4	3.3–19.7	5.9	2.6–15.9
≥2–<3 mm	2.9	1.3–7.2	3	1.4–7.6	2	0.9–5.2	1.8	0.8–4.9
≥3–<4 mm	1.3	0.6–3.3	0.8	0.2–3.2	1.2	0.5–3.3	1.3	0.6–3.5
≥4 mm	1		1		1		1	
Left knee								
<1 mm	45.5	14.9–163.3	38.1	11.9–142.1	22.7	9.4–64.3	14.0	5.7–40.2
≥1–<2 mm	8.7	4.0–20.2	8.5	3.8–20.1	7.3	3.3–19.5	5.3	2.3–14.2
≥2–<3 mm	2.3	1.2–5.0	2.3	1.2–5.1	2.4	1.1–6.4	2.0	0.9–5.3
≥3–<4 mm	0.9	0.4–1.9	0.9	0.4–1.9	1.4	0.6–3.8	1.4	0.6–3.7
≥4 mm	1		1		1		1	

Adjusted ORs were calculated by multiple logistic regression analysis after adjustment for age and BMI.
mJSW, minimum joint space width; CI, confidence interval.

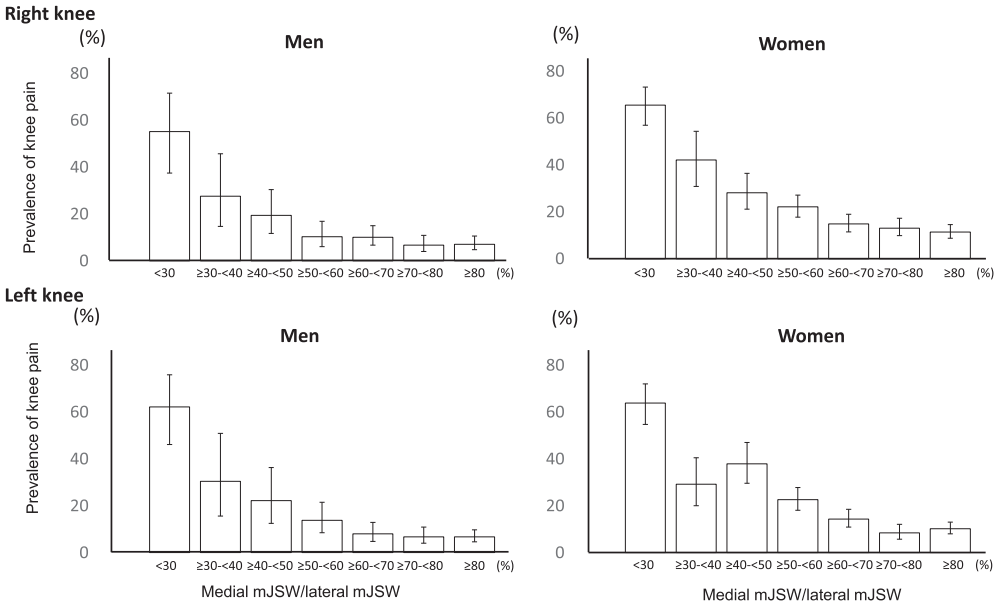

Fig. 2. Prevalence of knee pain by medial mJSW/lateral mJSW (%) in men and women. mJSW, minimum joint space width.

Table IV
OR of knee pain by the ratio of medial mJSW to lateral mJSW

	Men				Women			
	Crude OR	95% CI	Adjusted OR	95% CI	Crude OR	95% CI	Adjusted OR	95% CI
Right knee								
<30%	16.0	6.9–38.2	14.5	6.1–35.0	14.8	9.4–23.7	9.8	6.1–16.0
≥30–<40%	5.0	1.9–12.2	4.4	1.6–10.9	5.7	3.2–10.0	4.2	2.3–7.6
≥40–<50%	3.1	1.5–6.5	2.7	1.2–5.7	3.1	1.9–4.9	2.4	1.5–4.0
≥50–<60%	1.5	0.7–3.0	1.4	0.7–2.9	2.2	1.5–3.3	2.1	1.4–3.2
≥60–<70%	1.5	0.8–2.8	1.5	0.8–2.8	1.4	0.9–2.0	1.3	0.9–2.0
≥70–<80%	0.9	0.5–1.9	0.9	0.5–1.9	1.2	0.8–1.8	1.1	0.7–1.8
≥80%	1		1		1		1	
Left knee								
<30%	23.0	10.7–51.3	18.9	8.6–43.1	15.5	9.8–25.0	10.3	6.4–16.9
≥30–<40%	6.1	2.2–15.8	5.7	2.0–14.8	3.6	2.0–6.4	2.8	1.5–5.0
≥40–<50%	4.0	1.7–8.8	3.6	1.5–8.0	5.4	3.4–8.6	4.3	2.7–7.0
≥50–<60%	2.2	1.1–4.4	2.1	1.0–4.1	2.6	1.7–3.8	2.3	1.5–3.4
≥60–<70%	1.2	0.6–2.4	1.2	0.6–2.4	1.5	0.97–2.2	1.4	0.9–2.1
≥70–<80%	1.0	0.5–1.9	1.0	0.5–2.0	0.8	0.5–1.3	0.8	0.5–1.3
≥80%	1		1		1		1	

Adjusted ORs were calculated by multiple logistic regression analysis after adjustment for age and BMI.
mJSW, minimum joint space width; CI, confidence interval.

2 mm in women, while those of medial mJSW/lateral mJSW were approximately 60% in both men and women.

Although much effort has been devoted toward a definition of knee pain, the correlation with radiographic severity of knee OA was not as strong as one would expect[4,8–10]. In fact, our previous study showed that the OR of severe knee OA defined as KL grade 3 or 4 for knee pain was 8.6 in men and 4.4 in women[4], which was significant, but the OR was not as high as expected. One of the reasons for this is that knee pain may arise from a variety of structures other than joint cartilage, such as menisci, synovium, ligaments, bursae, bone, and bone marrow[26–30]. Another reason may be due to the definition of knee OA. Knee OA is characterized by the pathological features of joint space narrowing and osteophytosis. However, most conventional systems for grading radiographic severity have been categorical grades, such as KL grading[11], which cannot assess joint space narrowing individually. Several studies have shown that knee OA has a strong effect on QOL[31–34], but in these studies, knee OA was defined by categorical grades such as KL grade or American College of Rheumatology (ACR) grade, total knee arthroplasty, and self-questionnaire. In addition, joint space narrowing was separately evaluated using a radiographic atlas of individual features published by the Osteoarthritis Research Society International (OARSI) in 1995[35] and revised in 2007[36]. Chan *et al.* examined the association of joint space narrowing and duration of pain in patients with knee OA using categorical methods[14]. However, the grading is still limited in reproducibility and sensitivity due to the subjective judgment of individual observers and the categorical classification. Furthermore, because categorical methods are statistically less powerful than continuous methods, the association between pain and knee OA might have been underestimated in previous studies. Kinds *et al.* measured joint space width and found significant associations with clinical outcomes[16], but the threshold of joint space width for clinical outcomes remained unclear. In the present study, to overcome this problem, joint space width was evaluated using a fully automatic system, and the OR of mJSW <1 mm for knee pain was quite high, particularly in men, and it was possible to establish the threshold values of mJSW for knee pain, which may indicate that mJSW is better for diagnosing knee OA than KL grade. In the present study, 6% of men with mJSW <3 mm and 14% of women with mJSW <2 mm, which were the threshold values in the present study, had knee pain. In addition, our previous study showed that 10% of men without knee OA and 20% of women without knee OA had knee pain[4]. These subjects have knee pain, despite having no radiographical changes. This indicates that at least 10% and 20% of knee pain in men and women, respectively, may be explained by factors other than radiographical changes.

In the present study, sex differences were found in the association of mJSW with pain. These discrepancies between the sexes are explained by several factors. First, women are more susceptible to pain than men[4]. In fact, our previous study showed that the OR for knee pain in women without radiographic knee OA (KL = 0/1) was greater than that in men without radiographic knee OA[4]. In the present study, the prevalence of knee pain was 5–6% in men with mJSW ≥4 mm, while it was 7–9% in women with mJSW ≥4 mm. This high prevalence of knee pain in women with mJSW ≥4 mm, which are reference data, may partly explain the lower OR for knee pain in women than men. Second, men with normal knees had wider joint space widths than women with normal knees. Our previous study showed that mean mJSW in men with KL = 0 was approximately 4 mm, while that in women with KL = 0 was approximately 3 mm[25]. This means that subjects with mJSW = 3 mm have a normal knee in women, while they have joint space narrowing at the knee in men. In addition, mJSW = 1 mm means 75% cartilage loss in men, while it represent 67% cartilage loss in women. In fact, the associations of medial mJSW/lateral mJSW with pain were similar in men and women, which may also explain the lower OR for knee pain in women than men.

Obesity is one of the few established risk factors for knee OA and pain[17–23]. A clinical review article reported that 69% of knee replacements in middle-aged females can be attributed to obesity[22], and it has been estimated that, if overweight and obese individuals reduced their weight to reach normal BMIs, about 50% of knee OA cases would be eliminated[21]. However, to the best of our knowledge, there are no population-based studies that assess the effect of obesity on the association of joint space narrowing with pain. In the present study, a distinct effect of BMI was found on the association of mJSW with pain. For example, at the right knee in women, mJSW ≥1–<2 mm in women with BMI ≥23 kg/m^2 was significantly associated with pain, while mJSW ≥1–<2 mm in women with BMI <23 kg/m^2 was not, compared to mJSW≥4 mm with BMI <23 kg/m^2. In addition, the OR was similar between mJSW ≥1–<2 mm with BMI ≥23 kg/m^2 and mJSW <1 mm with BMI <23 kg/m^2. These indicate that weight loss may be an effective way to reduce knee pain even when joint space narrowing is present at the knee.

There are limitations in the present study. First, this was a large-scale, population-based, cross-sectional study of baseline data. Thus, causal relationships could not be determined. The ROAD study is a longitudinal survey, so further progress may help elucidate any causal relationships. Second, the threshold in the present study was calculated by a particular statistical method, but certain situations may favor sensitivity over specificity, e.g., screening. In addition, the sensitivity and specificity were modest in the present study. These may be partly explained by the fact that knee pain can arise from a variety of structures other than joint cartilage, such as menisci, synovium, ligaments, bursae, bone, and bone marrow[26–30], which are unable to be assessed radiologically. However, using the KOACAD system, it was possible to demonstrate strong associations of mJSW with knee pain and to establish the threshold of mJSW for knee pain, which may indicate that mJSW is more useful than categorical methods for diagnosing knee OA. Third, cases with lateral knee OA were excluded, leading to a selective sample. One reason for excluding lateral knee OA is that most knee OA in Japan is medial type. There are racial differences in the ratio of lateral to medial knee OA, and previous studies showed that the ratio of lateral to medial knee OA was 0.20 in Caucasian and 0.64 in Chinese populations[37]. In the Amsterdam OA Cohort, lateral knee OA is rather common, and it occurs in association with OA features in other knee compartments[38]. However, our previous study showed that the ratio of lateral to medial knee OA was 0.10 in Japan, which indicates that knee OA was medial type. The other reason for excluding lateral knee OA is that medial and lateral knee OA have distinct characteristics, because, in medial knee OA, there is narrowing of the medial mJSW, while in lateral knee OA, there is narrowing of the lateral mJSW. Thus, the effect of medial mJSW on pain may be obscured by lateral knee OA, because medial joint space width may not change or be larger in lateral knee OA. Thus, the aim of the present study was to clarify the effect of medial knee OA on pain, although excluding lateral OA leads to a selective sample. Lastly, it was not possible to clarify whether the threshold in the present study can apply to other races or populations, because the prevalence of knee OA and the ratio of medial knee OA/lateral knee OA are quite different among races[4,37,38], and the association of knee OA with pain among them may be quite different. To clarify this, international collaborative studies using the KOACAD system are needed.

In conclusion, the present cross-sectional study using a large population from the ROAD study showed that joint space narrowing was strongly associated with knee pain. The threshold of mJSW with knee pain was approximately 3 mm in men and 2 mm

in women, while the threshold of medial mJSW/lateral mJSW was approximately 60% in both men and women. BMI was found to have a distinct effect on the association of mJSW with pain. Further studies, along with continued longitudinal surveys in the ROAD study, will help improve our understanding of the mechanisms of joint space narrowing at the knee and their relationship with pain.

Acknowledgments

This work was supported by Grants-in-Aid for Scientific Research (S19109007, B20390182, C20591737, C20591774), for Young Scientists (A18689031), and for Exploratory Research (19659305) from the Japanese Ministry of Education, Culture, Sports, Science, and Technology, grants (H17-Men-eki-009, H18-Choujyu-037, H20-Choujyu-009, H21-Chouju-Wakate-011 and H22-Chouju-Wakate-007) from the Ministry of Health, Labour and Welfare, a Research Aid from the Japanese Orthopaedic Association (JOA-Subsidized Science Project Research 2006-1), and Grant No.166 from the Japan Orthopaedics and Traumatology Foundation.

The authors would like to thank Dr Anamizu and members of the Department of Orthopedics; Mr Kutsuma and other members of the Department of Radiology at Tokyo Metropolitan Geriatric Medical Center; Mrs Tomoko Takijiri and other members of the Public Office in Hidakagawa Town; and Mrs Tamako Tsutsumi and Mrs Kanami Maeda, and other members of the Public Office in Taiji Town, for their assistance in locating and scheduling participants for examinations.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2015.01.011.

Author contributions

All authors have made substantial contributions to all three of the following sections:

(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data;
(2) drafting the article or revising it critically for important intellectual content; and
(3) final approval of the version to be submitted.

Conflicts of interest

There are no conflicts of interest.

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